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Therapeutic equivalence of inhaled beclomethasone dipropionate with CFC and non-CFC (HFA 134a) propellants both delivered via the Easibreathe™ inhaler for the treatment of paediatric asthma

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Chlorofluorocarbon (CFC)-containing inhalers for use in the treatment of asthma are to be phased out under the terms of the Montreal Protocol (1). In this multi-centre, randomized, double-blind study, the therapeutic equivalence of two formulations of beclomethasone dipropionate (BDP) containing CFC or non-CFC (HFA134a) propellant, both delivered via the Easibreathe™ (Norton Healthcare Ltd, London, U.K.) inhaler, was determined in 229 asthmatic children. Each child received 100 μg doses of BDP (containing either CFC or HFA propellant) twice daily for 12 weeks.

Both CFC and HFA formulations produced statistically and clinically significant improvements in patient's lung function and symptom scores when administered via the Easibreathe™ inhaler. The improvements in mean morning peak expiratory flow (PEF) were 41 l min^{-1} and 34 l min^{-1} for the BDP-HFA and BDP-CFC products respectively ($P<0{\cdot}001$) and for mean evening PEF the improvements were 38 l min^{-1} and 38 l min^{-1}, respectively ($P<0{\cdot}001$). Similar findings were demonstrated for the other efficacy parameters. The two formulations were statistically equivalent with respect to efficacy. For mean morning PEF the estimated treatment difference (BDP-CFC/BDP-HFA ratio) was 102·6% (95% Cl 99·1, 106·2). Similar equivalence was shown for the other efficacy parameters. Both products were well tolerated, with no difference in the adverse event profiles, effects on 24 h urinary cortisol or *Candida* colonisation.

This study demonstrates that the new formulation of BDP with HFA-134a propellant is equivalent to and directly substitutable for BDP with the older CFC propellant in a dose for dose manner. This should enable a seamless transition from one product to the other when CFC containing products are eventually phased out. In addition this study has also shown that the Easibreathe™ inhaler is an effective delivery system for use with inhaled products for the treatment of asthma in children.

Key words: beclomethasone; Easibreathe™; HFA propellant; inhalation; paediatric asthma.

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Introduction

Beclomethasone dipropionate (BDP) is a corticosteroid indicated for the prophylactic management of asthma. Although the action of BDP is anti-inflammatory (2) and the exact mechanism of corticosteroid action within the lung is not fully understood, treatment with BDP reduces bronchial mucosal inflammation with consequent reduction of bronchial oedema and mucus secretion.

Treatment with BDP for the prophylactic management of asthma is invariably by inhalation. This is commonly via a pressurized metered-dose inhaler (pMDI). Currently, most pMDIs utilize a conventional chlorofluorocarbon (CFC) propellant to form an aerosol of BDP for inhalation. Under the terms of the Montreal Protocol (1), use of such CFC propellants is to be phased out due to their ozone depleting potential.

A CFC-free formulation of BDP has been developed (Norton Healthcare Ltd.) which utilizes 1,1,1,2-tetrafluoroethane, a hydrofluorocarbon propellant (commonly known as HFA-134a) and which is predicted to have

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minimal ozone depleting potential. The pharmacology and toxicology of this HFA molecule have been studied extensively by the International Pharmaceutical Aerosol Consortium for Toxicology Testing (IPACT-1). Further testing by pharmaceutical companies has shown that this propellant is free from any serious toxicity. Single- and multi-dose studies of HFA-134a in healthy humans have shown that it is well tolerated at dose levels well above those required for use in inhalation devices (3–5).

Other BDP products containing HFA-134a have recently been evaluated (6–8). These studies have shown that in combination with HFA-134a, beclomethasone dipropionate is as safe and as effective as the currently available CFC-containing products (6). Although a dose switch from CFC to CFC-free products is a desirable course of action, it has been suggested that due to the fine particle characteristics of the new formulations, it may be possible to reduce the effective dose by up to 50% (7,8). Whilst dose reduction has obvious clinical benefits, any such reductions must be closely supervised and should be carefully balanced against potential confusion that may be caused to the patient. The BDP formulation in this current study has been developed to allow a seamless dose for dose transition from CFC to CFC-free inhaler.

A novel breath-operated inhaler device (Easibreathe^{TM}) has been specifically designed to overcome the co-ordination problems patients experience when using standard pMDIs.

The aim of this study was to assess therapeutic equivalence and comparable safety of BDP-HFA and BDP-CFC both via Easibreathe^{TM} inhaler when administered to asthmatic children.

Patients and methods

PATIENTS

Asthmatic children aged 7–12 years (inclusive) were eligible for the study. Patients were recruited from 44 General Practice and Hospital sites in the U.K., South Africa, the Czech Republic, Yugoslavia and Hungary. All patients and their parent/guardian gave written informed consent to the child's participation. At baseline all patients were required to demonstrate a forced expiratory volume in 1 sec (FEV_1) of at least 60% of that predicted for their height and gender, and a reversibility of at least 10% in FEV_1 following inhalation of a standard 200 μg dose of salbutamol from a pMDI. Patients with a documented reversibility in FEV_1 of $\geq$10% recorded in the previous 12 months were also allowed to participate. Each patient was currently receiving an inhaled bronchodilator β_2-agonist and may also have been receiving sodium cromoglycate or nedocromil sodium (provided the dose remained constant throughout the study). Patients currently receiving inhaled corticosteroids or oral corticosteroids, or patients with unstable asthma, were excluded from the study. Patients with any significant medical or psychological conditions were also excluded.

Study design

This investigation was a randomized, double-blind, parallel group study. The patents were randomized in ascending numerical order at each site according to a predetermined random code generated by the Statwood Partnership. Eligible patients entered a 2 week placebo run-in period, during which they were instructed to take one puff twice daily from a CFC placebo Easibreathe^{TM} inhaler. Patients used a mini-Wright Peak Flow Meter^{TM} (Clement Clarke International Ltd., U.K.), to record twice daily PEF readings throughout the study. In addition patients also recorded daily use of relief bronchodilator and daytime and night-time asthma symptoms. At the end of the run-in period, each patient was required to have used relief bronchodilator (two puffs or more) on at least 3 days out of the last seven of the run-in period. Eligible patients were then randomized to receive either BDP-CFC or BDP-HFA at a dose of 100 μg twice daily via the Easibreathe^{TM} inhaler for the next 12 weeks. Data recorded on diary cards were the same as for the run-in period. Each patient re-attended the clinic at 1, 4, 8 and 12 weeks after randomization. At each visit assessments of lung function and emergent adverse events were made. Twenty four hour urinary cortisol measurements were made at the start and end of treatment in a sub-population ($\sim$20%) of the patients. Oropharyngeal swabs for *Candida albicans* were taken at the start and end of the study in all patients and where clinically indicated on symptomatic grounds throughout.

METHODS

Ethics committee approval was obtained as appropriate for each participating centre.

Measurement of lung function

Prior to taking any inhaled medication, patients were instructed to make three measurements of PEF on rising each morning, and again each evening before going to bed, using a mini-Wright Peak Flow Meter^{TM} (Clement Clarke International Ltd., Harlow, U.K.). All three recordings of PEF on each occasion were documented by the patients on diary cards. Spirometric assessments were made by the investigator at each clinic visit using a calibrated Micro spirometer^{TM} (Micro Medical Ltd., Rochester, U.K.). Local reference values were used.

Diary card data

Use of relief medication and symptom scores also were recorded twice daily. Patient's assessments of cough, wheeze and overall symptoms were recorded using 4-point (0–3) rating scales.

Safety assessments

These comprised clinical adverse events, 24 h urinary cortisol assessments (in approximately 20% of the patients) and presence of *C. albicans* on oropharyngeal swabs.

STATISTICAL METHODS

Sample size

To detect a mean difference of 25 l min^{-1} in morning PEF (10% of the expected level of 250 l min^{-1}) between treatments using a two-sided 95% confidence interval, 105 patients per treatment group were needed. This estimate assumed a standard deviation of 50 l/min^{-1} for each group and 90% power. To accommodate for dropouts and unevaluable patients, 130 patients were selected to be randomized to each treatment group.

Efficacy analysis

Mean morning PEF was calculated from the diary cards for weeks 11 and 12 of treatment. The data were subjected to an analysis of covariance to allow for the effect of treatment, using baseline measurements as covariate. Baseline was taken to be the mean value over the last week before randomization. A test for parallel slopes was carried out by looking at the treatment by baseline interaction. The student's *t*-test residuals were examined for normality by plotting the ranked values against their normal scores and for constant variance by plotting them against the fitted values. The ratio (expressed as percentage) of the two treatments (HFA/CFC) was estimated and 95% confidence intervals constructed. All other lung function parameters were analysed in the same manner. For all outcome variables, equivalence was declared when the 95% confidence interval for the ratio of treatment means relative to the CFC mean was completely contained within the interval (90%, 110%).

Symptom scores were analysed using Wilcoxon rank sums test. An estimate of the treatment difference, together with 95% confidence intervals was calculated using the Hodges–Lehmann method. No adjustment was made for baseline values.

Results

A total of 229 patients were recruited into the study of whom 199 provided evaluable data. Seven patients were withdrawn during the course of the study (four from the BDP-HFA group and three from the BDP-CFC group). Of these seven, two patients in each group were withdrawn for violation of the study protocol, two in the BDP-HFA group were withdrawn for unspecified reasons and one patient in the BDP-CFC group was withdrawn due to an exacerbation of asthma requiring hospitalisation. In addition 22 patients were excluded from the per-protocol analysis for violations of the study protocol and a further patient was excluded from the analysis as they had received less than 10 weeks of study medication. The efficacy analyses were carried out on the per-protocol sample of 199 patients (103 BDP-HFA and 96 BDP-CFC). Demographic details are given in Table 1.

The two treatment groups in the per-protocol analysis were well matched with respect to baseline lung function.

EFFICACY

Mean morning and evening PEF in both treatment groups increased over the study period and had reached a peak by week 10. For the per-protocol population these increases were statistically significant ($P < 0.001$) at all post-treatment time points (Fig. 1). The overall improvements in mean morning PEF were 41 l min^{-1} and 34 l min^{-1} for the BDP-HFA and BDP-CFC groups respectively. For mean evening PEF the corresponding values were 38 l min^{-1} and 32 l min^{-1}. The estimated treatment difference for mean morning PEF was 2·6% and the two treatments are thus equivalent (Table 2). Similarly equivalent results were obtained for mean evening PEF with the estimated treatment difference being 2·1%. Results for all of the other lung function parameters were also equivalent. The

TABLE 1. Demographic details (intent-to-treat population) and baseline lung function (per-protocol population)

		BDP-HFA	BDP-CFC	Total
Gender	Male	71 (61%)	75 (66%)	146 (64%)
	Female	45 (39%)	38 (34%)	83 (36%)
Age (years)	Median (Range)	10·0 (7·0–12·9)	9·8 (6·6–12·8)	9·9 (6·6–12·9)
Height (m)	Median (Range)	1·43 (1·13–1·72)	1·41 (1·17–1·66)	1·42 (1·13–1·72)
Weight (kg)	Median (Range)	34·6 (18·8–72·0)	33·0 (21·0–64·0)	34.8 (18·8–72·0)
PEF (l min^{-1})	Mean (SD)	308 (59·5)	305 (68·5)	
% Predicted PEF	Mean (SD)	96·4 (17·8)	95·3 (16·8)	
FEV_1(l)	Mean (SD	1·82 (0·45)	1·77 (0·42)	
% Predicted FEV_1	Mean (SD)	88·0 (15·0)	86·7 (13·9)	
% FEV_1	Mean (SD)	16·7 (6·5)	16·0 (8·0)	
Reversibility at baseline				

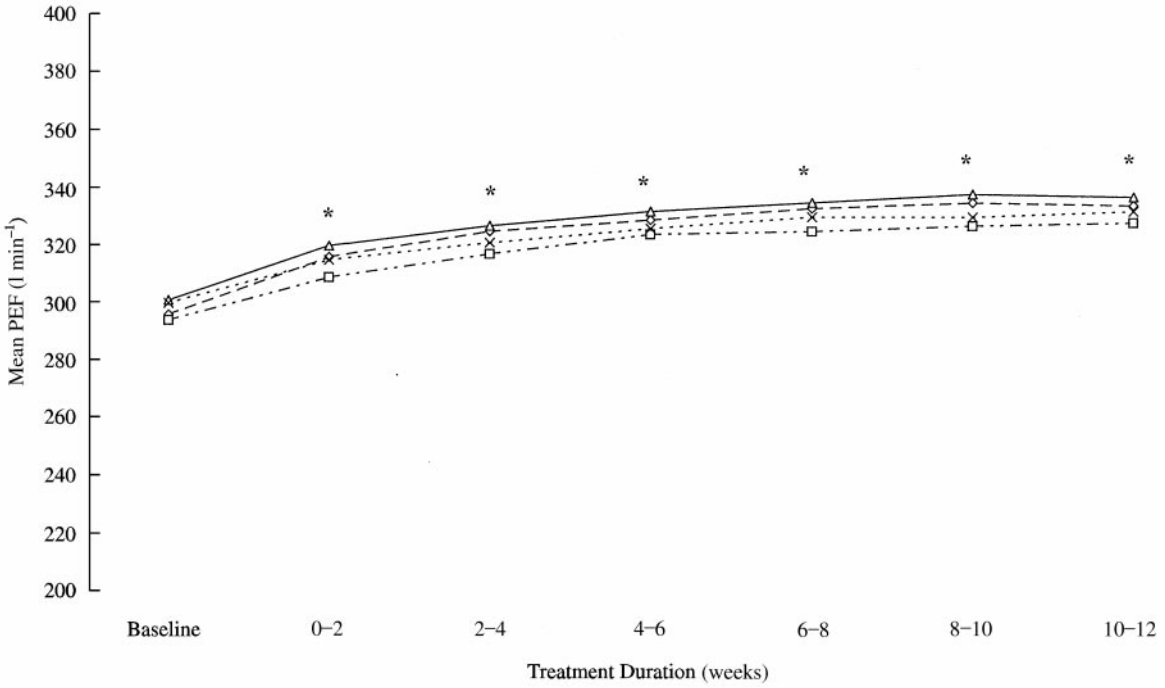

FIG. 1. Mean morning and evening PEF (Per-Protocol population) for each two weeks of the treatment period. All timepoints marked *were significantly different compared to baseline ($P < 0{\cdot}001$) .-◇-: BDP-HFA (am); -□-: BDP-CFC (am); -△-: BDP-HFA (pm); -X-: BDP CFC (pm).

TABLE 2. Analysis of lung function data (per-protocol population)

Parameter	Timepoint	BDP-HFA	BDP-CFC	Estimate (95% CI)—HFA/CFC(%)
Mean (SD)	Baseline	299 (56)	294 (62)	
morning PEF	Endpoint	340 (61)	328 (54)	
(l min^{-1})	Endpoint[1]	338	330	102·6 (99·1, 106·2)
Mean (SD)	Baseline	302 (57)	297 (61)	
evening PEF	Endpoint	340 (61)	329 (51)	
(l min^{-1})	Endpoint[1]	338	331	102·1 (998·6, 105·6)
Mean (SD) clinic	Baseline	308 (60)	305 (69)	
PEF	Endpoint	335 (59)	335 (59)	
(l min^{-1})	Endpoint[1]	337	333	101·2 (97·3, 105·1)
Mean (SD) clinic	Baseline	1·82 (0·45)	1·77 (0·42)	
FEV_1	Endpoint	1·98 (0·45)	1·90 (0·40)	
(l)	Endpoint[1]	1·97	1·91	103·5 (99·6, 107·5)
Mean (SD) daily	Baseline	20·8 (11·7)	22·3 (11·6)	
variability PEF	Endpoint	16·1 (13·6)	16·5 (10·9)	
(%)	Endpoint[1]	16·2	16·3	99·4 (78·6, 116·9)

[1]Least squares mean.

only exception to this was mean daily variability in PEF which decreased from 21–16% in the BDP-HFA group and from 22–16% in the BDP-CFC group.

Compared to baseline there were marked, significant decreases in the proportion of patients reporting daytime and night-time symptoms in both of the treatment groups and also in the proportion of patients using relief medication (Fig. 2). This is indicative of an overall improvement in asthma control for both treatments.

SAFETY

There was no preponderance of any one type of adverse event. No positive cultures for *C. albicans* were found at

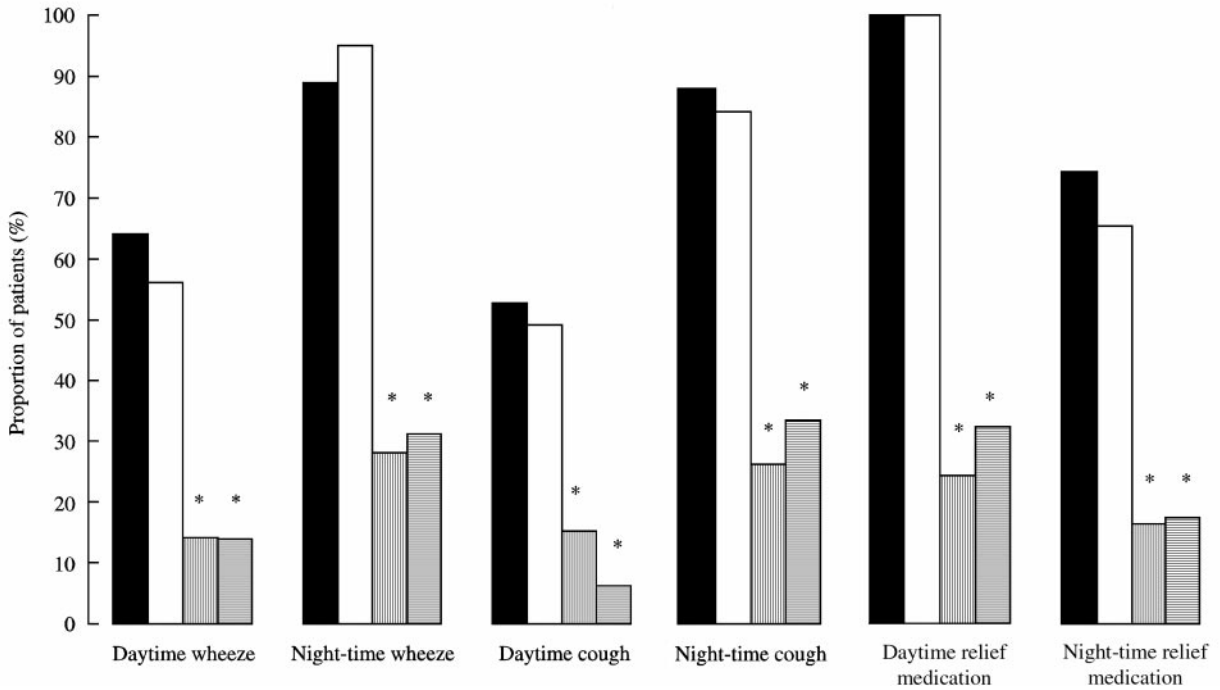

FIG. 2. Proportion of patients (%) reporting asthma symptoms and proportion (%) of patients using relief medication. *indicates significantly different to Baseline ($P < 0{\cdot}05$). There were no differences between treatments for the pre- or post-study values. ■: BDP-HFA pre-study; □: BDP-CFC pre study; ▥: BDP-HFA post-study; ▤: BDP-CFC post study.

baseline and at the end of study 13% of patients in the BDP-HFA group and 9% in the BDP-CFC group had positive cultures.

TWENTY FOUR HOUR URINARY CORTISOL

Mean baseline 24 h urinary cortisol values was assessed in 43/229 (19%) of patients and were comparable for both treatment groups (data from patients with only one measurement either pre- or post-study were excluded from this calculation). Mean baseline values were 129 nmol $24\,h^{-1}$ for BDP-HFA ($n = 24$) and 150 nmol $24\,h^{-1}$ for BDP-CFC ($n = 19$). The mean post-treatment values were 125 nmol $24\,h^{-1}$ and 121 nmol $24\,h^{-1}$ respectively. Individual patient data are presented in Fig. 3. The mean change for the BDP-HFA group was $-4{\cdot}6$ nmol $24\,h^{-1}$ and for the BDP-CFC group the mean change was $-28{\cdot}5$ nmol $24\,h^{-1}$.

Discussion

The introduction of new CFC-free propellants for asthma inhalers has presented healthcare professionals and the pharmaceutical industry with a number of unique challenges. Two main challenges are the determination of therapeutic equivalence between old and new products, and evolving strategies to manage the change over with respect to dosing levels and patient education.

In 1995 the British Association for Lung Research issued guidelines for the determination of equivalence for inhaled medication (9), but these did not define therapeutic equivalence. A more recent set of guidelines published by the Canadian Thoracic Society (10) gives detailed advice on the design and conduct of appropriate studies, but again falls short of a definition of therapeutic equivalence. This current study pre-dated publication of the Canadian report, but has included many of the recommendations that were proposed therein.

When designing studies to demonstrate therapeutic equivalence between asthma treatments it is important to show comparable improvement in asthma control with each, especially in patients who are steroid-naïve, as here. The study included a large number of patients with well defined asthma. Patients were thoroughly trained in inhaler use, the end points were consistent with the recommendations for establishing equivalence and the data were analysed to present 95% confidence intervals with a tight definition of equivalence.

This study has demonstrated that the newly formulated BDP-HFA inhaler is therapeutically equivalent to the existing BDP-CFC inhaler at a dose of 100 μg b.d. for the treatment of asthma in children requiring inhaled corticosteroids. This equivalence has been demonstrated for all objective parameters assessed in this study (with the exception of daily variability in PEF), with all of the 95%

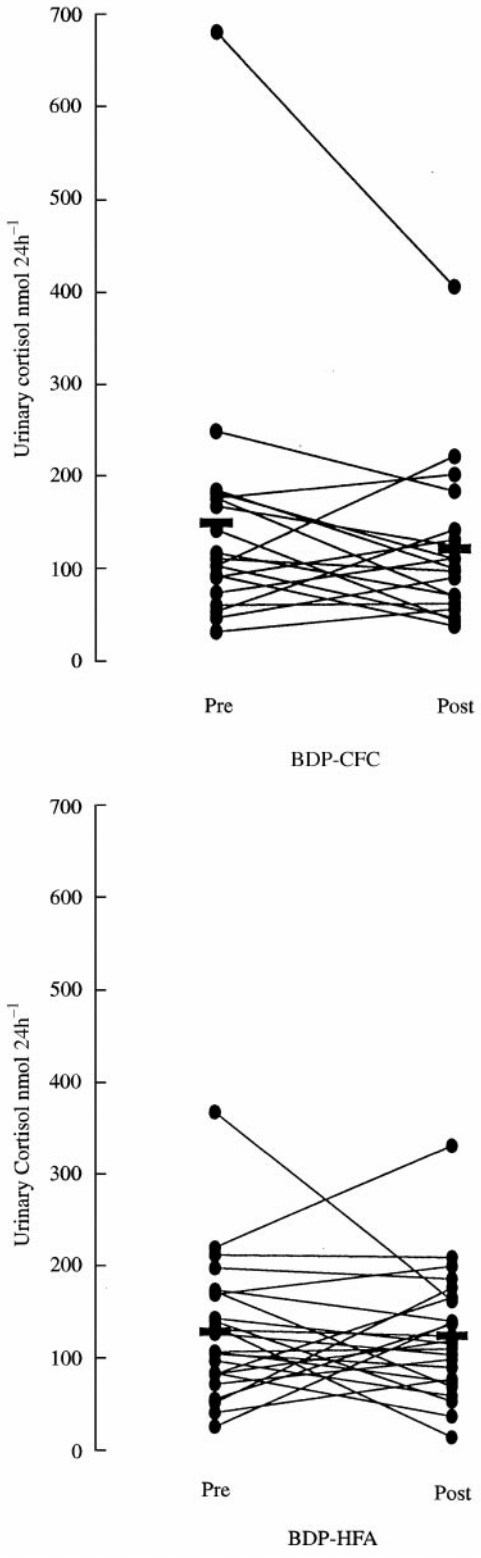

FIG. 3. Individual changes in 24 h urinary cortisol levels pre- and post-treatment (mean values are indicated by horizontal bars).

confidence intervals being completely within the range of 90–110%. The two treatments produced equivalent levels of efficacy in terms of effect on lung function and symptom control and had equivalent tolerability profiles. There was no evidence of any marked effects of either treatment on HPA function as assessed by 24 h urinary cortisol measurements, as might be expected at this dosage level for inhaled BDP. Mean changes in this parameter were greater if anything in the BDP-CFC group, at the end of the study.

For the primary efficacy endpoint, mean morning PEF, the estimated treatment difference was only 2·6%, which represents a difference in PEF between treatments of 8·5 l min^{-1}. The upper 95% Cl limit for this parameter showed a difference of 6·2%, representing a worst case difference between treatments of 20 l min^{-1}. Both formulations produced similar incidences of adverse events and these events were entirely consistent with those expected for a population of the type enrolled into this study.

Based on these results it appears possible to switch from a CFC to a CFC-free BDP formulation on a dose for dose basis. This is an important consideration which would facilitate a seamless transition to the new CFC-free inhalers for both clinicians and patients. Some recent studies have suggested that it may be possible to reduce the dose of corticosteroid by up to 50% when switching patients from BDP-CFC to BDP-HFA (7,8). This has been based upon the principle that, although the site of action for inhaled corticosteroids is not yet fully known, there is a greater fine particle deposition and penetration in the lung of BDP-HFA than BDP-CFC and that this correlates with enhanced efficacy. It may be argued conversely that an increase in fine particle penetration may lead to an increase in systemic absorption and subsequently an increase in adverse effects; further work is required in this respect. However, it is important to note that these dose reduction studies have not included direct comparisons at the same dose levels for BDP-CFC and BDP-HFA. In addition, results of these studies have been contradicted by a further study with the same formulation of BDP-HFA which showed a dose for dose equivalence (6). Two recent studies in adults (11) using the same formulation of BDP-HFA that was used in this current study also showed a dose for dose equivalence at both low and high doses further supporting the findings presented in this study. It is possible that the lack of a clinical difference between the HFA and CFC formulations may be a result of the relatively flat dose response curve seen with corticosteroids, although the fact that some studies have shown a clinical difference contradicts this.

In summary this study has shown that paediatric patients may be switched from currently available BDP-CFC inhalers to the new BDP-HFA inhalers at the same dose without loss of efficacy or asthma control, and with no changes in tolerability. In addition this study has also confirmed the effectiveness of the Easibreathe^{TM} inhaler in paediatric patients irrespective of the type of propellant used to deliver BDP.

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